



## Complete Summary

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### **GUIDELINE TITLE**

Diagnosis and management of polycystic ovarian syndrome.

### **BIBLIOGRAPHIC SOURCE(S)**

University of Texas, School of Nursing, Family Nurse Practitioner Program.  
Diagnosis and management of polycystic ovarian syndrome. Austin (TX):  
University of Texas, School of Nursing; 2006 May. 21 p. [45 references]

### **GUIDELINE STATUS**

This is the current release of the guideline.

## COMPLETE SUMMARY CONTENT

SCOPE  
METHODOLOGY - including Rating Scheme and Cost Analysis  
RECOMMENDATIONS  
EVIDENCE SUPPORTING THE RECOMMENDATIONS  
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS  
CONTRAINDICATIONS  
QUALIFYING STATEMENTS  
IMPLEMENTATION OF THE GUIDELINE  
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT  
CATEGORIES  
IDENTIFYING INFORMATION AND AVAILABILITY  
DISCLAIMER

## SCOPE

### **DISEASE/CONDITION(S)**

Polycystic ovarian syndrome

### **GUIDELINE CATEGORY**

Evaluation  
Management  
Treatment

### **CLINICAL SPECIALTY**

Endocrinology  
Family Practice

Internal Medicine  
Nursing  
Obstetrics and Gynecology

## **INTENDED USERS**

Advanced Practice Nurses  
Allied Health Personnel  
Nurses  
Patients  
Physician Assistants  
Physicians  
Psychologists/Non-physician Behavioral Health Clinicians  
Students

## **GUIDELINE OBJECTIVE(S)**

- To provide evidence-based practice guidelines for the evaluation and management of polycystic ovarian syndrome
- To enhance the immediate and long-term outcomes of patients with polycystic ovarian syndrome

## **TARGET POPULATION**

Women of reproductive age who meet the diagnostic criteria for polycystic ovarian syndrome, including ovulatory dysfunction (amenorrhea, infertility) and hyperandrogenism (hirsutism, virilization), and who are at risk for complications of polycystic ovarian syndrome (PCOS) (metabolic, cardiovascular, and cancer risks)

## **INTERVENTIONS AND PRACTICES CONSIDERED**

### **Evaluation/Diagnosis**

1. Subjective assessment including history and symptoms
2. Objective assessment/physical examination, including vital signs (blood pressure), height, weight, body mass index (BMI), waist to hip ratio, skin assessment for signs of hyperandrogenism and insulin resistance, thyroid assessment, breast exam, cardiovascular assessment, abdominal assessment, pelvic and bimanual exam, psychological assessment for presence of depression.
3. Laboratory tests, including serum follicle stimulating hormone (FSH), serum luteinizing hormone (LH), LH/FSH ratio, prolactin, 24-hour urine free cortisol, thyroid function tests: thyroid stimulating hormone (TSH), human chorionic gonadotropin (hCG), estradiol (E2), 17 hydroxyprogesterone, androgens, 2-hour 75-g oral glucose tolerance test (OGTT) if indicated, fasting lipid profile (FLP), atherogenic markers)
4. Diagnostic procedures
  - Pelvic ultrasound, preferably transvaginal ultrasound
  - Endometrial biopsy
5. Using Rotterdam Criteria for diagnosis

## **Management/Treatment**

1. Patient and family education
2. Non-pharmacological treatment
  - Diet, exercise, weight loss
  - Routine screening
  - Cosmetic therapies
3. Pharmacological treatment
  - Combined oral contraceptives (COC)
  - Medroxyprogesterone acetate
  - Insulin sensitizers (metformin) (Thiazolidinediones are considered but not recommended)
  - Antiandrogens (spironolactone, flutamide, finasteride)
  - Eflornithine
  - Ovulation inducers (clomiphene citrate, gonadotropins) (Tamoxifen is considered, but not recommended)
  - Lipid-lowering medications
  - Blood pressure lowering medications and aspirin
4. Surgery/Referral
  - Surgical laparoscopic ovarian drilling/electrocautery
  - Specialty referral
5. Follow up

## **MAJOR OUTCOMES CONSIDERED**

- Quality of life
- Efficacy of treatment
- Complications of polycystic ovarian syndrome (diabetes, ovarian and endometrial cancer, heart disease, infertility, depression)

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

### **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

Online searches were performed for dates January 2001 to January 2006 of the following databases: PubMed, Medline, CINAHL, Cochrane, and UpToDate (major keywords: polycystic ovary syndrome, PCOS, PCOS diagnostic tests, PCOS management, and PCOS medications). Position statements from the American Academy of Clinical Endocrinologists and the American College of Obstetricians and Gynecologists were also reviewed. Additional resources were identified by review of bibliographies of relevant articles and published guidelines.

### **NUMBER OF SOURCE DOCUMENTS**

Not stated

## **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Subjective Review

Weighting According to a Rating Scheme (Scheme Given)

## **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

**Quality of Evidence** (Based on U.S. Preventive Services Task Force Ratings)

- **Good:** Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
- **Fair:** Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.
- **Poor:** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

## **METHODS USED TO ANALYZE THE EVIDENCE**

Review of Published Meta-Analyses

Systematic Review

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

Journal articles were analyzed for quality based on type of study design, method, number of subjects, representative sample, generalizability of results, and applicability for target population.

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Not stated

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

**Strength of Recommendations** (Based on U.S. Preventive Services Task Force Ratings)

**A.** There is good evidence that the recommendation improves important health outcomes. Benefits substantially outweigh harms.

**B.** There is at least fair evidence that the recommendation improves important health outcomes. Benefits outweigh harms.

**C.** There is at least fair evidence that the recommendation can improve health outcomes but the balance of benefits and harms is too close to justify a general recommendation.

**D.** There is at least fair evidence that the recommendation is ineffective or that harms outweigh benefits.

**I.** Evidence that the recommendation is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

## **COST ANALYSIS**

Electrocautery may be more cost-effective compared to gonadotropins due to multiple pregnancy rates of gonadotropin use.

## **METHOD OF GUIDELINE VALIDATION**

Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

The guideline was developed by a group of family nurse practitioner (FNP) students and submitted for review to FNP program faculty and expert reviewers. Before submitting to the guideline committee, revisions were made based on reviewer recommendations.

## **RECOMMENDATIONS**

### **MAJOR RECOMMENDATIONS**

Strength of recommendations (A, B, C, D, I) and quality of evidence (good, fair, poor) are defined at the end of "Major Recommendations field."

### **Subjective Assessment/History and Symptom Analysis**

1. Chief complaint(s) and/or clinical manifestations
  - Reproductive
    - Menstrual cycle disturbances resulting from anovulation (e.g., oligomenorrhea, amenorrhea, dysfunctional uterine bleeding)
    - Obesity
    - Infertility
    - Hyperandrogenism (hirsutism, acne, androgenic alopecia)
    - Miscarriage
  - Metabolic
    - Impaired glucose intolerance
    - Type 2 diabetes mellitus
    - Cardiovascular disease
    - Gestational diabetes
    - Dyslipidemia
2. Review of systems
  - Constitutional: increase in weight, fatigue or anxiety, temperature intolerance

- Skin and hair: male pattern baldness, facial hair growth, acne, hyperpigmentation (axillae, nape of neck, under breasts, or skin flexures), dry skin, brittle hair and nails
  - Neck: change in neck size, noticing shirt collars feel tighter
  - Breasts: decrease in breast size, galactorrhea
  - Cardiovascular: hypertension, chest pain, shortness of breath, exertional dyspnea, exercise intolerance, ankle swelling
  - Abdomen: enlargement
  - Genitourinary: enlarged clitoris
  - Reproductive: amenorrhea, abnormal uterine bleeding
  - Endocrine: polydipsia, polyphagia, polyuria
  - Neurological: headache, visual disturbance
3. History of present illness
- Menstrual pattern, last normal menstrual period (LNMP)
  - Onset and duration of signs of androgen excess
  - Duration of infertility
  - Amount and duration of body weight changes
  - Lifestyle habits, such as diet, exercise, smoking, alcohol intake, drug use
4. Past medical history
- Growth and sexual development; onset of menarche
  - Hospitalizations/surgeries
  - Parity/infertility/miscarriage
  - Past diagnosis of diabetes
  - Past diagnosis of endometrial hyperplasia
5. Medication history
- Current prescription medications, including use of exogenous androgens
  - Current over-the-counter medications/herbal remedies
  - Allergies
6. Family history
- Polycystic ovarian syndrome (PCOS)
  - Obesity
  - Thyroid disease
  - Infertility/miscarriage
  - Diabetes
  - Cardiovascular disease
  - Dyslipidemia
7. Psychosocial history
- Sexual history; contraceptive methods used
  - Symptoms of depression and/or anxiety
  - Support systems, coping strategies

(Costello, 2005; Sheehan, 2004; Schroeder & ACOG, 2003; Hart, Hickey, & Franks, 2004; Richardson, 2003)

## **Objective Assessment/Physical Examination**

1. Vital signs (blood pressure): higher incidence of hypertension (American Association of Clinical Endocrinologists Polycystic Ovary Syndrome Writing Committee [PCOSWC], 2005)
2. Height, weight, body mass index (BMI): 25-30 = overweight; >30 = obese
3. Waist-hip ratio to determine body fat distribution: >0.72 = abnormal
4. Skin exam: assess for signs of hyperandrogenism (hirsutism, acne, androgenic alopecia or male-pattern baldness) and signs of insulin resistance (acanthosis nigricans in the axillae, nape of neck, under breasts, or skin flexures)
5. Neck exam: assess for thyroid enlargement
6. Breast exam: assess for decrease in breast size
7. Cardiovascular: assess for signs of cardiovascular disease (hypertension, abnormal heart sounds, decreased peripheral pulses, lower extremity edema)
8. Abdominal exam: assess for striae (Cushing's syndrome), enlargement, masses
9. Pelvic exam/bimanual exam: assess for loss of vaginal rugae, clitoromegaly, and enlarged uterus/ovaries
10. Neurological exam: assess for visual impairment (pituitary tumor)
11. Psychological exam: administer Zung depression scale if indicated

(American College of Obstetricians and Gynecologists [ACOG] Practice Bulletin, 2003; Costello, 2005; Schroeder & American College of Obstetricians and Gynecologists [ACOG], 2003, Fraser & Kovacs, 2004)

## **Diagnostic Procedures**

1. Laboratory tests:
  - Human chorionic gonadotropin (hCG): to evaluate for intrauterine pregnancy; would be negative in clients with PCOS
  - Follicle stimulating hormone (FSH): to evaluate for menopause; typically slightly decreased or normal in clients with PCOS; if elevated concerns of post-menopause
  - Luteinizing hormone (LH): to evaluate for ovarian tumors; elevated in 50 to 60% of clients with PCOS; concern for ovarian tumor with decreased levels
  - LH/FSH ratio: to evaluate for premature primary ovarian failure; >2 in PCOS
  - Prolactin: to evaluate for pituitary tumors and Cushing's; slightly elevated in some women with PCOS (levels 20 to 200 micrograms/L)
  - 24-hour urine free cortisol: to evaluate for Cushing's; mild elevations in PCOS; if  $\geq 2$  times upper limit of normal, more consistent with Cushing's
  - Thyroid stimulating hormone (TSH): to evaluate for thyroid dysfunction; typically normal in clients with PCOS
  - Estradiol (E2): to evaluate for premature primary ovarian failure or prolactinoma; typically slightly decreased with PCOS
  - Androgens: to help confirm PCOS and exclude androgen producing tumors
    - Dehydroepiandrosterone sulfate (DHEA-S): to evaluate for Cushing's, ovarian tumor, or menopause; typically normal or slightly elevated with PCOS; concerns with moderate elevations (Cushing's or ovarian tumor) or decreased levels (menopause)

- Total testosterone: to evaluate for adrenal disorders or tumors; typically normal or slightly elevated with PCOS; moderate elevations (>200ng/dL) concerns for tumor
- Sex hormone binding globulin (SHBG): to evaluate for tumors; typically suppressed with PCOS; if levels elevated, concerns for tumor
- Free androgen index (FAI): typically elevated with PCOS
- 17 hydroxyprogesterone: to evaluate for adrenal tumor or ovarian cancer; decreased with PCOS; concerns with elevated levels
- 2-hour 75 g oral glucose tolerance test (OGTT) if BMI  $\geq$ 28: to evaluate for glucose intolerance or diabetes mellitus
- Fasting lipid profile (FLP): to evaluate for hyperlipidemia secondary to hyperandrogenism; may be elevated with PCOS
- C-reactive protein (CRP), fibrinogen, homocysteine: may be elevated since PCOS patients have higher incidence of proinflammatory and atherogenic markers than non-PCOS patients placing them at higher risk for cardiovascular disease (CVD) (PCOSWC, 2005).

(Costello, 2005; ACOG Practice Bulletin, 2003; Sheehan, 2004)

## 2. Diagnostic procedures:

- Pelvic ultrasound, preferably transvaginal ultrasound: frequently shows ovaries of increased size due to either a greater number of follicles/cysts (12 or more follicles measuring 2 to 9 mm in diameter) or an increased ovarian volume. Findings may be nonspecific, as in women taking oral contraceptive pills, in non-obese women, or in women without symptoms of anovulation or hyperandrogenism (Balen et al., 2003; Costello, 2005; ACOG Practice Bulletin, 2003; Allemand et al., 2006; Hassan & Killick, 2003; Hart, Hickey, & Franks, 2004).
- Endometrial biopsy: unopposed estrogen from chronic anovulation (greater than 5 months) puts PCOS patients at higher risk for endometrial hyperplasia and cancer (Fraser & Kovacs, 2004; Richardson, 2003).

## Criteria for Diagnosis

1. Rotterdam Criteria: two of the following, in addition to exclusion of related disorders:
  - Oligo- or anovulation
  - Clinical and/or biochemical signs of hyperandrogenism
  - Polycystic ovaries

(The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004)

## Differential Diagnoses

1. Androgen secreting tumors of the ovary or adrenal gland
2. Hypogonadotropic hypogonadism (nutrition, excessive exercise, chronic disease)
3. Pituitary tumor and other prolactin disorders
4. Cushing's syndrome

5. Nonclassic congenital adrenal hyperplasia
6. Acromegaly
7. Genetic defects in insulin action
8. Primary hypothalamic amenorrhea
9. Primary ovarian failure
10. Thyroid disease
11. Exogenous androgens

(ACOG Practice Bulletin, 2003; Sheehan, 2004; Lane, 2006; Schroeder & ACOG, 2003)

## Management

Management techniques are individualized to patient symptoms and goals. Overall treatment factors include ovulation induction, normalization of the endometrium, prevention of symptomatic hyperandrogenism, and reduced insulin resistance (Buccola & Reynolds, 2003).

### Step 1 – Patient and Family Education

1. Explain diagnosis. PCOS is a heterogeneous condition caused by many factors and involves several genes. Much of the pathophysiology is not fully understood. Hypotheses include the following: 1) dysfunction of gonadotropin-releasing hormone and luteinizing hormone resulting from hypothalamic-pituitary abnormalities; 2) enzyme defect in ovarian and adrenal steroid production; 3) metabolic dysfunction characterized by insulin resistance and compensatory hyperinsulinemia that adversely affect the hypothalamus, pituitary, ovaries, and adrenal glands. Infertility is due to impaired follicular development associated with FSH deficiency. Teaching should include contraception methods since return of fertility is an expected goal of treatment (PCOSWC, 2005; Van der Spuy & Dyer, 2004; Fraser & Kovacs, 2004). **Evidence Fair, Recommendation C**
2. Explain risks associated with PCOS.
  - Increased cardiovascular risk results from several mechanisms including changes in blood vessel function, abnormal coagulation, elevated atherogenic markers (CRP, fibrinogen, homocysteine), decreased antioxidant capacity, elevated serum lipids, and hypertension (Cattrall & Healy, 2004; PCOSWC, 2005; ACOG Practice Bulletin, 2003; Sheehan, 2004). **Evidence Fair, Recommendation C**
  - Patients with PCOS are at increased risk for type 2 diabetes (risk is as high as 5 to 10 times that of general population). Age of onset occurs as early as 3rd or 4th decade. 30% of women with PCOS have impaired glucose tolerance (Cattrall & Healy, 2004). **Evidence Fair, Recommendation C**
  - Cancer risk linked to PCOS has not been demonstrated with good quality of evidence; however, there appears to be a higher risk for endometrial, breast, and ovarian cancer in PCOS patients. The main theory that supports increased cancer risk involves that of unopposed estrogen stimulation (Cattrall & Healy, 2004; Fraser & Kovacs, 2004). **Evidence Fair, Recommendation C**

- Pregnancy-related risks include infertility, miscarriage, and gestational diabetes. The exact pathogenesis of miscarriage is not clearly defined, and appears to be the result of several interrelated factors, including elevated LH levels, hyperandrogenemia, insulin resistance, obesity, and abnormal follicular growth (Jakubowicz et al., 2002; Nestler et al., 2002; ACOG Practice Bulletin, 2003) **Evidence Fair, Recommendation C**
  - Depression and anxiety are long-term risks of PCOS due to infertility and negative cosmetic effects (Richardson, 2003). **Evidence Fair, Recommendation C**
3. Establish treatment goals. Return of menses and fertility, absence of hirsutism, and prevention of complications. **Evidence Fair, Recommendation C**

## Step 2 – Non-pharmacological Treatment

1. Diet, exercise, weight loss. Treatment should begin with lifestyle modification with emphasis on controlled eating patterns (reduced fat intake and increased fiber) and regular aerobic exercise to achieve weight control. This is the best first line intervention for patients with a BMI greater than 26. Weight loss from lifestyle modification alone has caused resumption of regular menstruation, decreased LH levels, induction of ovulation, improved fertility, decreased androgens, improvement of insulin resistance, and decreased risk for diabetes and cardiovascular disease. Smoking cessation should also be addressed to reduce cardiovascular risk. Weight reduction may minimize long-term cancer risk (ACOG Practice Bulletin, 2003; PCOSWC, 2005; Pasquali et al. 2003; Guzick, 2004; Cattrall & Healy, 2004; Sheehan, 2004). **Evidence Fair, Recommendation A**
2. Routine screening. All patients should be screened for hypertension, glucose intolerance with 2-hour 75g OGTT, and for dyslipidemia with fasting lipid profile (FLP) (ACOG Practice Bulletin, 2003; PCOSWC, 2005). **Evidence Good, Recommendation A**
3. Cosmetic therapies. Options for hirsutism include bleaching, plucking, shaving, electrolysis, and laser therapy; these are effective to some degree. These may involve significant expense, localized skin irritation and scarring, and long term time commitment (Buccola & Reynolds, 2003; Sheehan, 2004; PCOSWC, 2005). **Evidence Fair, Recommendation B**

## Step 3 – Pharmacological Treatment

There are no U.S. Food and Drug Administration (FDA)-approved drugs indicated for the treatment of PCOS, and any drug intervention will be an off-label application (Yildiz, 2004).

1. Combined oral contraceptives (COC): Appropriate for first-line treatment and long-term management. Mechanisms of action include suppression of LH secretion from the pituitary and increased circulating SHBG. Treatment is aimed at suppressing hyperandrogenism, restoring menstrual regularity, preventing endometrial hyperplasia, preventing pregnancy, possibly improving lipid levels, and treating acne and hirsutism (ACOG Practice Bulletin, 2003; PCOSWC, 2005). Controversy exists regarding COCs as first line use in PCOS due to their detrimental effect on insulin sensitivity, and this

- is currently being studied (Morin-Papunen et al., 2003). Additionally, use of non-androgenic 3rd-generation progestins, such as norgestimate or desogestrel, or anti-androgens, such as drospirenone, is recommended as they have shown to cause less detrimental effects on glucose, insulin, and lipids. (Yildiz, 2004; Bruni et al., 2003). Further studies are warranted though as it is unknown currently whether certain oral contraceptives are better than others (ACOG Practice Bulletin, 2003). **Evidence Fair, Recommendation B**
2. Medroxyprogesterone acetate: 10 mg for 7 to 10 days every (Q) 1 to 3 months. Action: to induce menses, reduce endometrial hyperplasia, and restore menstrual regularity. This treatment does not affect androgen levels, yet normalizes endometrial growth and therefore prevents the associated risk for endometrial cancer (Lane, 2006; Stout & Fugate, 2005; Richardson, 2003). **Evidence Good, Recommendation B**
  3. Insulin sensitizers: to improve insulin sensitivity, inhibit gluconeogenesis, improve menstrual regularity and ovulation, and reduce androgen synthesis. These also act synergistically with clomiphene for inducing ovulation and menstrual regularity.
    - Metformin: improves hyperinsulinemia, hyperandrogenism, menstrual cyclicity and causes ovulation. Through reducing insulin levels there is decreased insulin-mediated ovarian androgen production, increased SHBG synthesis (which insulin blocks from the liver), reduced LH/FSH ratio, reduced LH, reduced 17-OHP, and decreased levels of free androgens (Tan, Yap, & Tan, 2001; Genazzani et al., 2004). Positive effects on pregnancy have been demonstrated in a prospective case control study (Glueck et al., 2002). A retrospective study reported lower incidence of first-trimester pregnancy loss with metformin use (Jakubowicz et al., 2002). There are less pronounced effects on hirsutism than COCs or antiandrogens. Not FDA approved for PCOS, but much support in medical literature. Metformin does improve cardiovascular risk factors which also lends support to its use. Long-term safety and effectiveness is yet to be demonstrated (Cattrall & Healy, 2004; Sheehan, 2004; Kelly & Gordon, 2002; Nestler, et al., 2002; Pasquali et al., 2003; PCOSWC, 2005; ACOG Practice Bulletin, 2003; Lord, Flight, & Norman, 2003). **Evidence Good, Recommendation B**
    - Thiazolidinediones (TZDs) (pioglitazone and rosiglitazone): Another class of insulin-sensitizers that are less well-studied. Improved hyperinsulinemia-mediated ovarian androgen production, decreased plasma and free testosterone levels, and increased sex hormone binding globulin (SHBG) levels (Tan, Yap, & Tan, 2001). TZDs have been shown to improve hyperandrogenism and cause ovulatory cycles, but their use is considered investigational at this time (Stout & Fugate, 2005; PCOSWC, 2005). A recent randomized controlled trial (RCT) showed pioglitazone to be as effective as metformin in improving insulin resistance and hyperandrogenism in women with PCOS, however, pioglitazone caused increases in body weight, BMI, and waist to hip ratio (Ortega-Gonzalez et al., 2005). Troglitazone was shown to improve hirsutism by 17% but has since been removed from the market due to liver toxicity (Azziz et al., 2001). **Evidence Poor, Recommendation I**
  4. Antiandrogens: The following antiandrogens have all proven effective treatment alone for hirsutism so their use is indicated if COC use is contraindicated, although birth control is needed as all have teratogenic

potential. When used with COC, antiandrogens work synergistically by suppressing androgen levels through different mechanisms.

- Spironolactone (50 to 200 mg/d) possesses intrinsic hormonal activity and interferes with steroidogenesis.
- Flutamide (250 mg/day) acts at the androgen receptor sites as a pure antiandrogen
- Finasteride (2.5 to 5 mg/day) 5-alpha-reductase inhibitor for treatment of androgenic alopecia; blocks the enzyme responsible for converting testosterone to its active metabolite dehydrotestosterone. Low dose (2.5 mg) as effective as high dose (5 mg) (Bayram et al., 2002; ACOG Practice Bulletin, 2003; PCOSWC, 2005; Christy, Franks, & Cross, 2005). **Evidence Fair, Recommendation C**

5. Eflornithine: Topical agent for hirsutism, inhibits the enzyme ornithine decarboxylase. Slows hair growth, but does not remove hair. Has not been studied specifically in PCOS patients, but has been proven effective for treatment of unwanted facial hair for women. Is well-tolerated with notable benefit after 6 months of use. Not covered by insurance, so cost may be an issue. (Sheehan, 2004; ACOG Practice Bulletin, 2003; Balfour & McClellan, 2001). **Evidence Good, Recommendation B**

6. Ovulation inducers to provide pharmacological levels of FSH:
- Clomiphene citrate: 50 to 100 mg/day for 5 days at beginning of cycle. Restores menstrual regularity, prevent endometrial hyperplasia and induce ovulation by stimulating the release of pituitary gonadotropins. Traditional first-line treatment for anovulatory women who wish to conceive. 80% will ovulate in response to treatment, and 50% of those will conceive. Of those who respond, 50% do so with the 50-mg daily starting dose, another 20% with the 100-mg daily dose. Pregnancy response usually occurs within the first six ovulatory cycles. Prolonged duration of treatment does not significantly increase rate of pregnancy, however, adding another agent can increase ovulation rates (ACOG Practice Bulletin, 2003). **Evidence Good, Recommendation B**
  - Combination of clomiphene with metformin is more effective than either agent used alone to restore ovulation and achieve pregnancy. In patients who are resistant to clomiphene, metformin may also be effective in restoring responsiveness to clomiphene (Costello, 2005; George et al., 2003; Kocak et al., 2002; Nestler et al., 2002; Vandermolen et al., 2001).

### **Evidence Good, Recommendation B**

- Tamoxifen: 5 to 40 mg/day for 4 days at beginning of cycle. Non-steroidal selective estrogen receptor modulator. Not FDA approved for ovulation induction (off-label use). Shown to have similar efficacy as clomiphene in a controlled observational study (Nardo, 2004).

### **Evidence Poor, Recommendation I**

- Exogenous gonadotropins:
  - Urinary follicle stimulating hormone (uFSH) (Metrodin ®) and recombinant FSH (rFSH) (Gonal F® and Puregon®). Both uFSH and rFSH are equally effective in inducing ovulation in women who are resistant to clomiphene; uFSH has smaller amounts of urinary proteins which lowers incidence of adverse reactions

(local allergy or hypersensitivity). Risks of both include multiple follicle development, multiple pregnancies and ovarian hyperstimulation syndrome; risks can be reduced by using lower doses. Lower dosing has also been shown to be more effective. The most frequently used dosing schedules are low dose step up and step down regimens. Higher costs are associated with rFSH (Bayram, van Wely, & van der Veen, 2001; ACOG Practice Bulletin, 2003). **Evidence Fair,**

**Recommendation B**

- Human menopausal gonadotropin (hMG). Contains FSH, luteinizing hormone (LH) and large quantities of potentially allergenic urinary proteins. Has been associated with increased risk of ovarian hyperstimulation syndrome (Bayram, van Wely, & van der Veen, 2001; Tan, Yap, & Tan, 2001). **Evidence Fair, Recommendation C**

7. Lipid-lowering medications: Suppression of androgens is associated with elevated lipids. When dietary and exercise measures have been tried first, then use of appropriate medications is warranted (statin, fibrate, niacin, ezetimibe, or some combination of these medications) (ACOG Practice Bulletin, 2003; PCOSWC, 2005). **Evidence Fair, Recommendation B**
8. Blood pressure lowering medications and aspirin: Treat elevated blood pressure with appropriate medications, and add aspirin as appropriate for reduction of cardiovascular risk (PCOSWC, 2005). **Evidence Good, Recommendation A**

#### **Step 4 – Surgery / Referral**

1. Surgical laparoscopic ovarian drilling/electrocautery: Laparoscopic electrocautery of the ovaries is effective for ovulation induction. This procedure is indicated for patients resistant to or suffering side effects with clomiphene citrate, patients in whom gonadotropin therapy has failed, or patients with ovarian hyperstimulation from either clomiphene or gonadotropins. When comparing electrocautery to gonadotropin therapy (rFSH), there have been no differences shown in ovulation rates, pregnancy rates, live birth rates, or miscarriage rates. There is a lower risk of multiple pregnancies with electrocautery. Studies have also shown that ovarian electrocautery resulted in decreased resistance to clomiphene citrate and greater efficacy of recombinant FSH following surgery. Electrocautery may be more cost-effective due to multiple pregnancy rates of gonadotropin use. Risks include adhesion formation, and potential surgical risks (bleeding and infection) anesthesia risks, and premature ovarian failure (theoretical complication) (Bayram et al., 2004; Farquhar et al., 2002; Farquhar, 2004; Farquhar et al., 2005). **Evidence Good, Recommendation B**
2. Referral to specialist: Specialty referral depends on the expertise of the clinician. Consider referral under the following circumstances:
  - Abnormal unexplained vaginal bleeding or very heavy bleeding
  - Anovulatory dysfunctional bleeding not responding to medications
  - Suspicion of other hyperandrogen disorders needing exclusion
  - Severe hyperlipidemia
  - Diagnosis of type 2 diabetes
  - Recurrent miscarriages

- Infertility management, especially when other factors co-exist, such as male infertility
- Patient intolerant of usual treatments
- Treatment failure

(Costello, 2005)

3. Patient resources/support groups/therapists

- PCOS Association, Inc. (support group chapters available by state)

PO Box 80517, Portland, OR. 97280, 1(877) 775-7267

[www.pcosupport.org](http://www.pcosupport.org)

- The Hormone Foundation [www.hormone.org](http://www.hormone.org)

1(800) HORMONE (1-800-467-6663)

- American Fertility Association (national therapist referral list available)

[www.theafa.org](http://www.theafa.org)

- Androgen Excess Society [www.androgenexcesssociety.org](http://www.androgenexcesssociety.org)
- American Association of Clinical Endocrinologists [www.aace.com](http://www.aace.com)

## **Step 5 – Follow Up**

Follow up depends on individual signs and symptoms and treatment regimens

1. Regular follow up every 6 months to monitor weight, blood pressure, fasting glucose and lipids
2. Breast exam, Pap smear, mammogram as recommended for all women
3. Anti-androgen therapy: every 3 to 6 months initially
4. Progestin therapy for anovulatory dysfunctional uterine bleeding: every 3 to 6 months initially
5. In women trying to conceive, if no pregnancy occurs after 6 months, additional infertility evaluations are performed. When no pregnancy occurs 9 to 12 months after return of ovulation, intrauterine insemination is considered if appropriate, then gonadotropins and in vitro fertilization.

(Fraser & Kovacs, 2004; Guzick, 2004) **Evidence Fair, Recommendation B**

See "PCOS Tracking Flowchart" in the original guideline document for follow up and outcomes measurement tool

## **Definitions:**

**Quality of Evidence** (based on U.S. Preventive Services Task Force Ratings)

- **Good:** Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes
- **Fair:** Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.
- **Poor:** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

#### **Strength of Recommendations** (based on U.S. Preventive Services Task Force Ratings)

**A.** There is good evidence that the recommendation improves important health outcomes. Benefits substantially outweigh harms.

**B.** There is at least fair evidence that the recommendation improves important health outcomes. Benefits outweigh harms.

**C.** There is at least fair evidence that the recommendation can improve health outcomes but the balance of benefits and harms is too close to justify a general recommendation.

**D.** There is at least fair evidence that the recommendation is ineffective or that harms outweigh benefits.

**I.** Evidence that the recommendation is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

#### **CLINICAL ALGORITHM(S)**

None provided

### **EVIDENCE SUPPORTING THE RECOMMENDATIONS**

#### **REFERENCES SUPPORTING THE RECOMMENDATIONS**

[References open in a new window](#)

#### **TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS**

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

These guidelines are based on sources such as research studies (randomized controlled trials, retrospective cohort studies, prospective case studies, case control studies, and controlled observational studies), meta-analysis reviews, systematic literature reviews, expert opinion, and practice guidelines and position

statements from professional organizations (American College of Obstetricians and Gynecologists Practice Bulletin, and American Association of Clinical Endocrinologists position statement).

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

- Improved identification and management of patients with polycystic ovary syndrome
- Improved quality of life for patients with polycystic ovary syndrome:
  - Return of menses
  - Return of fertility
  - Absence of hirsutism
  - Prevention of complications (obesity, diabetes, cancer, heart disease, pregnancy complications, and depression)

### POTENTIAL HARMS

- Adverse effects of medications (see original guideline document for more information)
- *Cosmetic therapies* may involve significant expense, localized skin irritation and scarring, and long term time commitment.
- Risks of *electrocautery* include adhesion formation, and potential surgical risks (bleeding, infection, and anesthesia risks), and premature ovarian failure (theoretical complication).

## CONTRAINDICATIONS

### CONTRAINDICATIONS

- *Combined oral contraceptives* are contraindicated in patients with previous thromboembolic event or stroke; current or past history of cerebrovascular or coronary artery disease; valvular heart disease with complications; severe hypertension; diabetes with vascular involvement; history of estrogen-dependent tumor; headache with focal neurological symptoms; known or suspected breast cancer; personal history of breast, endometrial, or hepatic cancer; liver disease; known or suspected pregnancy; undiagnosed abnormal uterine bleeding; hypertriglyceridemia; being over the age of 35 and smoking heavily; concomitant anticonvulsant drug therapy; major surgery with prolonged immobilization; and known hypersensitivity to drug.
- *Medroxyprogesterone acetate* is contraindicated in known or suspected pregnancy or as a diagnostic test for pregnancy; undiagnosed abnormal uterine bleeding; known or suspected breast cancer; active thrombophlebitis; current or past history of thromboembolic disorders or cerebral vascular disease; liver disease; and known hypersensitivity to drug.
- *Metformin* is contraindicated in renal disease or renal dysfunction (serum creatinine  $\geq 1.5$  in males or  $\geq 1.4$  in females); congestive heart failure requiring pharmacologic management; liver disease; excessive alcohol intake; acute or chronic metabolic acidosis with or without coma (including diabetic ketoacidosis); and known hypersensitivity to drug. Metformin should be

discontinued temporarily in patients undergoing radiologic studies with intravenous iodine contrast.

- *Spironolactone* is contraindicated in anuria; acute renal insufficiency; significant renal impairment; hyperkalemia; and known hypersensitivity to drug.
- *Flutamide* is contraindicated in severe hepatic impairment; known or suspected pregnancy; and known hypersensitivity to drug.
- *Finasteride* is contraindicated in known or suspected pregnancy (pregnant women should not even handle medication); and known hypersensitivity to drug.
- *Eflornithine* is contraindicated in concomitant coumarin-type anticoagulant therapy or history of deep vein thrombosis or pulmonary embolus; and known hypersensitivity to drug.
- *Clomiphene citrate* is contraindicated in known or suspected pregnancy; liver disease; undiagnosed abnormal uterine bleeding; ovarian cysts or enlargement not due to polycystic ovarian syndrome (PCOS); uncontrolled thyroid or adrenal dysfunction; organic intracranial lesion such as pituitary tumor; and known hypersensitivity to drug.
- *Gonadotropins* are contraindicated in patients with a high follicle stimulating hormone (FSH) level indicating primary ovarian failure; uncontrolled thyroid and adrenal dysfunction; an organic intracranial lesion such as a pituitary tumor; sex hormone dependent tumors of the reproductive tract and accessory organs; undiagnosed abnormal uterine bleeding; ovarian cysts or enlargement not due to PCOS; known or suspected pregnancy; and known hypersensitivity to drug.
- *Lipid-lowering medications*: Refer to prescribing information for individual lipid-lowering medications. Contraindications for statin use include active liver disease; unexplained persistent elevations of serum transaminases (>3 times upper limit of normal); known or suspected pregnancy; breast-feeding; known hypersensitivity to drug. Contraindications for fibrate use include hepatic or severe renal dysfunction including primary biliary cirrhosis and unexplained persistent liver function abnormalities; pre-existing gallbladder disease; and known hypersensitivity to drug.
- *Blood pressure lowering medications and aspirin*: Refer to prescribing information for individual antihypertensive medications. Aspirin contraindications include asthma; nasal polyps; bleeding disorders; use in children (<16 years of age) for viral infections; known or suspected pregnancy; and known hypersensitivity to drug.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- These guidelines are not intended for use outside of the stated population.
- The skill and judgment of the health care provider must dictate treatment decisions.
- These guidelines provide a general framework for managing patients with polycystic ovarian syndrome (PCOS), who typically have varying symptoms and goals. The major recommendations are not intended to be utilized all inclusively, and decisions must be based on individual symptoms and goals.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

### IMPLEMENTATION TOOLS

Chart Documentation/Checklists/Forms

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness  
Patient-centeredness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

University of Texas, School of Nursing, Family Nurse Practitioner Program.  
Diagnosis and management of polycystic ovarian syndrome. Austin (TX):  
University of Texas, School of Nursing; 2006 May. 21 p. [45 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2006 May

### GUIDELINE DEVELOPER(S)

University of Texas at Austin School of Nursing, Family Nurse Practitioner Program  
- Academic Institution

### SOURCE(S) OF FUNDING

University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program

## **GUIDELINE COMMITTEE**

Practice Guidelines Committee

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## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

No relationships exist between the guideline developers and any for-profit and not-for-profit companies or organizations that could potentially influence the contribution to the guideline development.

## **GUIDELINE STATUS**

This is the current release of the guideline.

## **GUIDELINE AVAILABILITY**

Electronic copies: None available.

Print copies: Available from the University of Texas at Austin, School of Nursing.  
1700 Red River, Austin, Texas, 78701-1499

## **AVAILABILITY OF COMPANION DOCUMENTS**

A polycystic ovarian syndrome (PCOS) tracking flowchart is available with the original guideline document.

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This NGC summary was completed by ECRI on October 17, 2006. The information was verified by the guideline developer on November 14, 2006.

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